Abstract

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The cDNA sequence encoding porcine brain
natriuretic peptide and related genes encoding canine and
human peptides with natriuretic activity are disclosed.
The gene is shown to make accessible the DNAs encoding
analogous natriuretic peptides in other vertebrate species.

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The genes encoding these NPs can be used to effect
modifications of the sequence to produce alternate forms of
the NPs and to provide practical amounts of these proteins.
The NPs of the invention can also be synthesized
chemically. The invention peptides have the formula:

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$$R^1\text{-Cys-Phe-Gly-Arg-}\genfrac{}{}{0pt}{}{\text{Arg/}}{\text{Lys}}\text{ - }\genfrac{}{}{0pt}{}{\text{Leu/}}{\text{Met}}\text{ -Asp-Arg-}$$

$$\genfrac{}{}{0pt}{}{\text{Ile- Gly/}}{\text{Ser}}\text{ -Ser- }\genfrac{}{}{0pt}{}{\text{Leu/}}{\text{Ser}}\text{-Ser-Gly-Leu-Gly-Cys-}R^2 \qquad (1)$$

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wherein R^1 is selected from the group consisting of:

(H);

Gly-;

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Ser-Gly-;

$$\genfrac{}{}{0pt}{}{\genfrac{}{}{0pt}{}{\text{Asp/}}{\text{Lys/}}}{\text{Gly}}\text{ -Ser-Gly-;}$$

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$$\genfrac{}{}{0pt}{}{\genfrac{}{}{0pt}{}{\text{Arg/}}{\text{His/}}}{\text{Gln}}\text{ - }\genfrac{}{}{0pt}{}{\genfrac{}{}{0pt}{}{\text{Asp/}}{\text{Lys/}}}{\text{Gly}}\text{ -Ser-Gly-;}$$

$$\genfrac{}{}{0pt}{}{\text{Met/}}{\text{Val}}\text{ - }\genfrac{}{}{0pt}{}{\genfrac{}{}{0pt}{}{\text{Arg/}}{\text{His/}}}{\text{Gln}}\text{ - }\genfrac{}{}{0pt}{}{\genfrac{}{}{0pt}{}{\text{Asp/}}{\text{Lys/}}}{\text{Gly}}\text{ -Ser-Gly-;}$$

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			Arg/	Asp/	
Thr/	- Met/	- His/	- Lys/	-Ser-Gly-;
Met	Val	Gln	Gly	

			Arg/	Asp/	
Lys-	Thr/	- Met/	- His/	- Lys/	-Ser-Gly-;
	Met	Val	Gln	Gly	

			Arg/	Asp/	
Pro-Lys-	Thr/	- Met/	- His/	- Lys/	-Ser-Gly-;
	Met	Val	Gln	Gly	

			Arg/	Asp/	
Ser-Pro-Lys-	Thr/	- Met/	- His/	- Lys/	-Ser-Gly-;
	Met	Val	Gln	Gly	

or a 10- to 109-amino acid sequence shown as the native
upstream sequence for porcine, canine or human BNP in
Figure 8, or a composite thereof;

R^2 is (OH), NH_2, or NR'R" wherein R' and R" are
independently lower alkyl (1-4C) or is

Asn/
Lys

Asn/ -Val
Lys

Asn/ -Val-Leu
Lys

Asn/ -Val-Leu-Arg
Lys

Asn/ -Val-Leu-Arg- Arg/
Lys   Lys

Asn/ -Val-Leu-Arg- Arg/ - Tyr/
Lys   Lys   His

or the amides (NH_2 or NR'R") thereof,
with the proviso that if formula (1) is

R^1-Cys-Phe-Gly-Arg-Arg-Leu-Asp-Arg-
   Ile-Gly-Ser-Leu-Ser-Gly-Leu-Gly-Cys-R^2

and R^1 is Asp-Ser-Gly-, R^2 cannot be Asn-Val-Leu-Arg-Arg-Tyr.

5   The peptides of the invention can be formulated into pharmaceutical compositions and used to treat conditions associated with high extracellular fluid levels, especially congestive heart failure.

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